PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference ACADIA.033VP	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/004765	International filing date *(day/month/year)* 18 February 2004 (18.02.2004)	Priority date *(day/month/year)* 19 February 2003 (19.02.2003)]
International Patent Classification (IPC) or national classification and IPC [7] C07D 239/22, A61K 31/513, C07C 225/18, C07D 231/06, 239/26, 281/10, A61K 31/135, 31/415, 31/505, 31/554		
Applicant ACADIA PHARMACEUTICALS INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- ☒ Box No. I — Basis of the report
- ☒ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 19 August 2005 (19.08.2005)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

REC'D 29 NOV 2004
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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/004765	18.02.2004	19.02.2003

International Patent Classification (IPC) or both national classification and IPC
C07D239/22, A61K31/513, C07C225/18, C07D231/06, C07D239/26, C07D281/10, A61K31/135, A61K31/415,

Applicant
ACADIA PHARMACEUTICALS INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/004765

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/004765

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/004765

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2-5, 6-12 (all partly), 14-18, 19-33 (all partly)

because:

☒ the said international application, or the said claims Nos. 25-32 (as regards industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 2-5, 6-12 (all partly), 14-18, 19-33 (all partly)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/004765

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 6-12 (all partly), 13, 19-33 (all partly)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 6-12 (all partly), 13, 19-33 (all partly)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1, 6-12, 13, 19-33
Industrial applicability (IA)	Yes:	Claims	1, 6-12 (all partly), 13, 19-24 (all partly), 33 (partly)
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/004765

Re Item III.

The present **claims 25-32** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect to industrial applicability of the subject-matter of this claim.
[For the assessment of the aforesaid claim on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a (known) *compound for* first *use in medical treatment* and the *use* of such a compound *for the manufacture of a medicament* for a new medical treatment.]

Re Item IV.

The present application lacks unity within the meaning of Rule 13 PCT for the following reasons:

The document J. Med. Chem. **45**(23), 4950-4953 (2002) (**D1**) discloses (cf., page 4951, column 1, scheme 1) the compound **AC-7954** which is said to have *urotensin II agonistic activity* (cf., page 4951, column 1, last paragraph)(cf., e.g., pages 133-134, table 1).

In the light of **D1**, the **problem** underlying the present application resides in the provision of <u>further</u> (alternative) *urotensin II agonists*.

Accordingly, the present application proposes

(i) the 5-(2-aminoethyl)-*5,6-dihydro-3H-pyrimidin-2-one* derivatives of the present formula I (cf., the present compound **claim 1**),

(ii) the 1-(2-aminoethyl)-*cyclopropane* derivatives of the present formula II (cf., the present compound **claim 2**),

(iii) the 4-(2-aminoethyl)-*4,5-dihydro-1H-pyrazole* derivatives of the present formula III (cf., the present compound **claim 3**),

(iv) the 5-(2-aminoethyl)-*pyrimidine* derivatives of the present formula IV (cf., the present compound **claim 4**), and

(v) the 3-(2-aminoethyl)-*2,3-dihydro-benzo-[b]-[1,4]-thiazepine* derivatives of the present formula V (cf., the present compound **claim 5**)

in order to solve the given problem.

The only structural feature discernible, which is shared by all of the compounds according to the present formulae (I) - (V) is the

R_3R_7N-$CH(R_4)$-$CH(R_5)$- substituted ring

(wherein R_3 - R_5 and R_7 are as defined in the present claim 1).

The document **D1**, however, already teaches the compound 3-(4-Chlorophenyl)-3-(2-(dimethylamino)ethyl)isochroman-1-one comprising this structural element (cf., the ***3-(2-(dimethylamino)ethyl) substituted isochromane*** for the *same use* as the compounds of the present application.

As the only structural feature which is common to all of the present compounds (i.e., the R_3R_7N-$CH(R_4)$-$CH(R_5)$- substituted ring) is not novel (cf., **D1**), this structural feature cannot represent the "special technical feature" within the meaning of Rules 13.1 and 13.2 PCT.

The present application thus relates to different solutions to the given technical problem (i.e., the provision of <u>further</u> *urotensin II agonists*) which are not linked by a single general inventive concept as set forth in Rule 13 PCT).
Hence it is considered that the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept:

1. the compounds of the present general **formula I**, which differ from the compound **AC-7954** of **D1** in that the 2-aminoethyl group is attached to a *5,6-dihydro-3H-pyrimidin-2-one* ring rather than an *isochroman-1-one* ring (cf., the present **claims 1**, **6-12** (**all partly**), **13** and **19-33** (**all partly**));

2. the compounds of the present general **formula II**, which differ from the compound **AC-7954** of **D1** in that the 2-aminoethyl group is attached to a *cyclopropane* ring rather than an *isochroman-1-one* ring (cf., the present **claims 2**, **6-12** (**all partly**) and **17-33** (**all partly**));

3. the compounds of the present general **formula III**, which differ from the compound **AC-7954** of **D1** in that the 2-aminoethyl group is attached to a *4,5-dihydro-1H-pyrazole* ring rather than an *isochroman-1-one* ring (cf., the present **claims 3**, **6-12** (**all partly**), **14** and **17-33** (**all partly**));

4. the compounds of the present general **formula IV**, which differ from the compound **AC-7954** of **D1** in that the 2-aminoethyl group is attached to a *pyrimidine* ring rather than an *isochroman-1-one* ring (cf., the present **claims 4**, **6-12** (**all partly**), **15** and **19-33** (**all partly**));

5. the compounds of the present general **formula V**, which differ from the compound **AC-7954** of **D1** in that the 2-aminoethyl group is attached to a *2,3-dihydro-benzo-[b]-[1,4]-thiazepine* ring rather than an *isochroman-1-one* ring (cf., the present **claims 5**, **6-12** (**all partly**), **16** and **17-33** (**all partly**));

As no additional search fee has been paid, the International Search Report has been limited to the subject-matter as defined under item 1 above, i.e., to the compounds of the present **formula I**, the method for their preparation, pharmaceutical compositions comprising them, and their use as medicaments (cf., the present **claims 1**, **6-12** (**all partly**), **13**, **19-33** (**all partly**).

As the International Search Report forms the basis of this Written Opinion, the following statement on the patentability of the present subject-matter can only be regarded as being complete in respect of the present **claims 1** and **13** (the present **claims 6-12** and **19-33** have only been examined as far as the compounds of **formula I** are concerned).

In so far as the following letter refers to **claims 6-12** and **19-33** it should only be taken to refer to the searched scope of these claims.

Re Item V.

The following documents are considered to be relevant:

D1: ..... Journal of Medicinal Chemistry **45**(23), 4950-4953 (7 November 2002);
D2: ..... Organic Letters **5**(9), 1551-1554 (1 May 2003);

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document.
If it later turns out that this is not correct, the document **D2** as cited in the International Search Report could become relevant.

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1, 6-13** and **19-33** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The compounds of the present independent **claim 1** are novel over the prior art **D1** on account of the *5,6-dihydro-3H-pyrimidin-2-one* ring (cf., the *isochromanon-1-one* ring of the compound **AC-7954** of **D1**).

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the **full scope** of the **claims 1**, **6-13** and **19-33** does not appear to involve an inventive step (Rule 65(1)(2) PCT):

The document **D1** - which represents the **closest prior art** - discloses (cf., page 4951, column 1, scheme 1) the compound **AC-7954** which is said to have *urotensin II agonistic activity* (cf., page 4951, column 1, last paragraph)(cf., e.g., pages 133-134, table 1).

The compounds of the present independent **claim 1 differ** from the said compound **AC-7954** essentially in that they are 5-(2-aminoethyl)-*5,6-dihydro-3H-pyrimidin-2-one* derivatives rather than 3-(2-aminoethyl)-*isochromanon-1-one* derivatives.

In the light of **D1**, the **problem** underlying the present application resides in the provision of further (alternative) *urotensin II agonists*.

Accordingly, the present application proposes the compounds of the present **claim 1** in order to **solve** the given problem.

Given the structural differences between the prior art compound **AC-7954** (cf., the *isochromanon-1-one* ring) and the present 5-(2-aminoethyl)-*5,6-dihydro-3H-pyrimidin-2-one* derivatives, it is considered that the person skilled in the art could not have predicted that the present 5-(2-aminoethyl)-*5,6-dihydro-3H-pyrimidin-2-one* derivatives would (also) possess *urotensin II agonistic activity*.
It is therefore considered that those compounds of the present **claim 1** which actually solve the give problem are regarded to be non-obvious in the light of the prior art.

Having regard to (i) the prior art **D1** and (ii) the presently tested compound of the example 2 it is considered that it has not been made credible yet that **essentially all** of the presently claimed compounds represent a solution to the underlying problem.
It would appear from **D1** and the presently tested example that the presence of (i) a *dialkylaminoethyl* group (cf., the broad definitions of the present substituent groups R_3 - R_5 and R_7 and the use of the term "optionally substituted") and (ii) a *4-chlorophenyl* group (cf., the broad definition of the present substituent group R_6) is essential for the *urotensin II agonistic activity*.

It is therefore considered that the *urotensin II agonistic activity* has not been made credible yet for the **full scope** of the present compound **claims 1** and **6-13**

Accordingly, an inventive step cannot be acknowledged (yet) for the **full scope** of the present the **claims 1, 6-13** and **19-33** (Article 33(3) PCT).

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1, 6-13, 19-24** and **33** concerns chemical compounds, a chemical process and a pharmaceutical composition and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

4.1. The document **D1** should have been cited (Rule 5.1(a)(ii) PCT).

4.2. The explanation of the term "C_{3-8}-cycloalkyl" (cf., page 7, lines 16-18 and 24-27) - as far as the presence of "one or more unsaturated bonds" is concerned - does not correspond with the usual meaning of this term (the person skilled in the art would not understand the term "cycloalkyl" as used in the present claims as also including "cyclo*alkenyl* groups).
The same observation applies mutatis mutandis to the explanation of the terms "aryl" and "heteroaryl" as given on page 8. The person skilled in the art would not understand these terms as also referring to aryl and heteroaryl groups "...optionally carrying *one or more substituents* selected from halogen, hydroxy, amino, etc....".
These passages thus create inconsistencies between the claims and the description, which lead to a doubt concerning the extent of protection afforded by the claims, thus rendering the claims unclear (Article 6 PCT).